Preparation and properties of optically active ethyl 2-isothiocyanato carboxylates

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Received 18 January 1979

Six antipodal ethyl 2-isothiocyanato carboxylates synthesized by the thiophosgene method were subjected to circular dichroic measurement.

Методом кругового дихроизма было изучено шесть антиподных этил-2-изотиоцианатокарбоксилатов, синтезированных по тиофосгенному методу.

Antipodal alkyl 2-isothiocyanato carboxylates were already prepared by dithiocarbamate method [1], D- and L-alanine and D- and L-leucine, as well as L-valine and L-glutamic acid being the starting material. The obtained isothiocyanates were isolated by g.l.c. chromatography and characterized by ORD curves [2].

The synthesis and spectral properties of racemates of 2-isothiocyanato carboxylates [3, 4], measurement of their dipole moments [5], and kinetic studies of reactivity towards nucleophilic reagents [6] were stimulated by the effort to clear the interaction of isothiocyanate and alkoxycarbonyl groups in α position. As found, they influence each other by intramolecular donor-acceptor interaction and consequently, they exist in two limit conformations.

Bearing these results in mind, we synthesized and investigated three enantiomeric pairs of isothiocyanates of general formula $R-CH(NCS)CO_2C_2H_5$, where $R = i\text{-}C_3H_7$ (*I*, *II*), $CH_2CO_2C_2H_5$ (*III*, *IV*), $C_6H_5CH_2$ (*V*, *VI*), the starting material being the respective ethyl amino acid hydrochlorides. Thiophosgenation in this procedure did not take place at the chiral centre and therefore, no inversion of configuration of the amino acid moiety could be anticipated.

The relatively high yields of all isothiocyanates were obtained after a 10 h reaction time and a minimum excess of thiophosgene applied concurrently with a reagent for binding of hydrogen chloride. Pure products obtained by column chromatography did not afford polymeric products during distillation under diminished pressure. The purity of the synthesized isothiocyanates was checked by thin-layer chromatography. The individual R_f values (Table 1) are an average of two measurements.

Table 1

Characterization of the synthesized isothiocyanates

Compound	Configuration	Formula	*M*	Calculated/found			Yield %	B.p. °C/Pa	R_f	$[\alpha]_D^{25b}$	
				% C	% H	% S				deg	conc %
I	L	$C_8H_{13}NO_2S$	187.26	51.31	6.99	17.12	87	50.0—51.0/0.3[a]	0.53	− 2.4	5
				51.30	7.05	16.99					
II	D			51.31	6.99	17.12	86	50.6—51.0/0.3	0.57	+ 2.8	5
				51.35	6.93	17.04					
III	L	$C_9H_{13}NO_4S$	231.29	46.80	5.61	13.85	81	38.5—39.0/0.3	0.42	−49.4	1
				46.95	5.52	13.70					
IV	D			46.80	5.61	13.85	83	36.5—37.5/0.1	0.43	+59.6	1
				46.81	5.81	13.75					
V	L	$C_{12}H_{13}NO_2S$	235.31	61.25	5.56	13.63	71	38.5—39.5/0.1	0.52	−62.4	1
				61.09	5.43	14.01					
VI	D			61.25	5.56	13.63	75	39.5—40.0/0.3	0.54	+70.2	1
				61.14	5.48	13.89					

a) Ref. [2] does not give constants; *b*) in *n*-hexane.

Table 2

UV and CD spectral data

Compound	Configuration	UV λ/nm (log ε)[b]	CD $\lambda(\Delta\varepsilon)$[b]
I	L		253 (0.21)
		273 (3.09)	
II	D		252 (−0.35)
V	L		227 (+2.01) 255[a] (−0.09)
		220 (3.70) 248 (3.06) 258 (2.92)	269 (−0.08) 268 (−0.12)
		252[a] (3.06) 265[a] (263)	
VI	D		225 (−2.72) 255 (+0.13)
			263 (+0.19) 260 (+0.16)

a) Shoulder; *b*) in *n*-hexane.

Measured were the CD curves of both ethyl 2-isothiocyanato-3-methylbutyrates (*I*, *II*) and 2-isothiocyanato-3-phenylpropionates (*V*, *VI*). As shown (Table 2), D forms are optically more pure. Compounds *I* and *II* displayed antipodal dichroic bands at about 250 nm due to the presence of an −NCS grouping. Compounds *V* and *VI* have, in addition to the −NCS group also a benzyl group attached to the chiral centre, so that besides of long-wave bands in the 250—270 nm region of the u.v. spectrum also short-wave bands at about 220 nm were observed. These bands relate to Cotton effects of different sign in the spectrum of circular dichroism. Compound *V* revealed long-wave dichroic bands of negative and a short-wave one of positive signs.

Experimental

Amino acids were commercially available (Lachema, Brno and Nutritional Biochemicals Corporation). Thiophosgene was purified according to [3], ethyl amino acid hydrochlorides were obtained by esterification in an excess of anhydrous ethanol saturated with gaseous hydrogen chloride [7—11]. All optically active compounds were purified by recrystallization from a suitable mixture of solvents and dried at 0.1 Pa and 60°C for several hours prior to measurement.

The respective isothiocyanates were prepared in a 100 ml vessel (Fig. 1) equipped with a stopcock at the bottom (*1*), a side tube for a thermometer (*2*), a jacket (*3*), a stirrer (*4*), and an adapter (*5*) serving for simultaneous addition of thiophosgene and saturated $NaHCO_3$ solutions. This arrangement avoids an unpleasant smell of thiophosgene during the reaction and separation of isothiocyanates. It also enables syntheses at low temperatures. The synthesized isothiocyanates were chromatographed on thin layers of silica gel (Spolana, Neratovice) with 10% of plaster as a binder in the solvent system ethyl acetate−hexane (1.2 : 8.8) at room temperature. Samples were spotted as 0.5% $CHCl_3$ solutions and detected

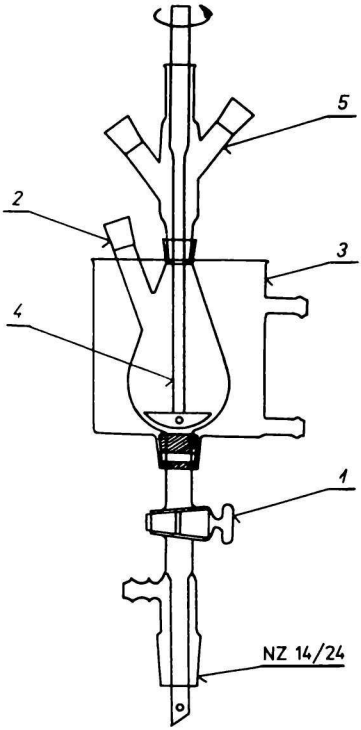

Fig. 1. Reactor for the preparation of isothiocyanates.

with aqueous $AgNO_3$ (5%) and ammonia (10%) and a subsequent 5 min heating at 140°C [12]. Optical rotations were measured with a Perkin—Elmer, model 141 polarimeter, the individual concentrations and solvents are given in Table 1. The CD curves were recorded with an ORD/UV-5 spectropolarimeter Jasco equipped with a CD adapter in 0.1—1.0 cm cells at a 5×10^{-2} mg/ml concentration and room temperature in a spectrally pure *n*-hexane (Merck).

Ethyl isothiocyanato carboxylates

Chloroform (10 ml) was added to a solution of the respective ethyl amino acid hydrochloride in water (10 ml) in the apparatus shown in Fig. 1 and thiophosgene (5% chloroform solution, 1.01 mole per 1 mole of the ester) and aqueous saturated $NaHCO_3$ were added during 2 h under vigorous stirring, thiophosgene being in a little excess. After 10 h, the chloroform solution containing the isothiocyanate formed was separed, washed with an aqueous solution of citric acid and water, dried with anhydrous Na_2SO_4, concentrated *in vacuo* and column-chromatographed on alumina (activity grade IV, isothiocyanate to alumina ratio 1 : 30). The chromatographically pure isothiocyanate was vacuum-distilled.

Data characterizing the synthesized isothiocyanates are listed in Table 1.

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Translated by Z. Votický